

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
16 June 2005 (16.06.2005)

PCT

(10) International Publication Number  
**WO 2005/053681 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 31/366**,  
31/336, 31/40, 31/405, 31/663, A61P 3/10, 19/00, A61K  
45/06

(21) International Application Number:  
PCT/GB2004/005019

(22) International Filing Date:  
29 November 2004 (29.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0327742.3 28 November 2003 (28.11.2003) GB

(71) Applicant (for all designated States except US): **ISIS IN-  
NOVATION LIMITED** [GB/GB]; Ewert House, Ewert  
Place, Summertown, Oxford, Oxfordshire OX2 7SG (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **SEWELL, Andrew**  
[GB/GB]; University of Oxford, Nuffield Department of  
Clinical Medicine, Peter Medawar Building, South Parks  
Road, Oxford OX1 3SY (GB).

(74) Agent: **LORD, Hilton, David**; Marks & Clerk, 90 Long  
Acre, London WC2E 9RA (GB).

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE,  
SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,  
GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(88) Date of publication of the international search report:  
13 October 2005

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: NOVEL USES OF MEVALONATE PATHWAY BLOCKERS

(57) Abstract: Statins are able to block the mevalonate pathway at an early stage, preventing build up of isopentenyl pyrophosphate by nitrogen containing bisphosphonates by blocking the pathway further downstream, with medicaments containing statins being administered at an appropriate time being able to thereby prevent the build up of IPP, which has been found to activate  $\gamma\delta$  T cells and cause the acute phase response associated with the nitrogen containing bisphosphonates.

WO 2005/053681 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/JP2004/005019

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/366 A61K31/336 A61K31/40 A61K31/405 A61K31/663  
A61P3/10 A61P19/00 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 127 573 A (PFIZER PRODUCTS INC) 29 August 2001 (2001-08-29) cited in the application paragraphs '0016!', '0017!; claims 1-5,9,10 paragraph '0021! paragraphs '0023! - '0036! paragraphs '0046! - '0048! paragraph '0059!	1-6,8-19
X	WO 99/45923 A (MERCK & CO., INC; FISHER, JOHN, E; RODAN, GIDEON, A) 16 September 1999 (1999-09-16) cited in the application page 1, lines 17-22; claims 1-13,16-19,23-25 pages 4-5; examples 2-6 ----- -/-	1-6,8-19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

Date of the actual completion of the international search

5 July 2005

Date of mailing of the international search report

03/08/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Kanbier, D

# INTERNATIONAL SEARCH REPORT

International Application No  
PC1/GB2004/005019

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STEWART G ET AL: "Delayed gastrointestinal complications associated with alendronate: A case involving an elderly nursing home resident" CANADIAN JOURNAL OF HOSPITAL PHARMACY 2000 CANADA, vol. 53, no. 5, 2000, pages 346-348, XP008049461 ISSN: 0008-4123 page 346, left-hand column, paragraph 3 - page 347, left-hand column, paragraph 1 -----	1,2,4,5, 8-12,14, 15,18,19
X	YLITALO R: "Bisphosphonates and atherosclerosis" GENERAL PHARMACOLOGY: VASCULAR SYSTEM 2000 UNITED STATES, vol. 35, no. 6, 2000, pages 287-296, XP002268656 ISSN: 0306-3623 page 288, right-hand column, paragraph 5 - page 290, left-hand column, paragraph 1 -----	1,2,5, 11-15,19
X	US 2001/034364 A1 (GASPER SHIRLEY R ET AL) 25 October 2001 (2001-10-25) example 8 -----	1,2,4, 9-19
A	GALLACHER ET AL: "Side-effects of pamidronate" LANCET, 1989, page 42, XP008049438 cited in the application the whole document -----	1-10,14, 19
A	ADAMI ET AL: "The acute-phase response after bisphosphonate administration" CALCIFIED TISSUE INTERNATIONAL, vol. 41, 1987, pages 326-331, XP008049432 cited in the application page 330, left-hand column -----	1-10,14, 19
P,X	WO 2004/024165 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; BAULCH-BROWN, CINDY, MAREE; SPENCER) 25 March 2004 (2004-03-25) page 2, paragraph 1; examples 1-5,7 page 8, paragraph 6 - page 9, paragraph 2 pages 9-11; claims -----	1-6,8-19
T	MARIANI S ET AL: "Effector 'gamma!'delta! T cells and tumor cells as immune targets of zoledronic acid in multiple myeloma" LEUKEMIA 2005 UNITED KINGDOM, vol. 19, no. 4, 2005, pages 664-670, XP008049442 ISSN: 0887-6924 page 668, right-hand column -----	14

# INTERNATIONAL SEARCH REPORT

ational application No.  
PCT/GB2004/005019

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 19 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB2004/005019

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1127573	A	29-08-2001	BR 0100558 A	11-09-2001
			CA 2337381 A1	15-08-2001
			EP 1127573 A1	29-08-2001
			JP 2001253827 A	18-09-2001
			US 2001036936 A1	01-11-2001
WO 9945923	A	16-09-1999	AU 2901199 A	27-09-1999
			CA 2323448 A1	16-09-1999
			EP 1061917 A1	27-12-2000
			JP 2002506030 T	26-02-2002
			WO 9945923 A1	16-09-1999
			US 2001025028 A1	27-09-2001
US 2001034364	A1	25-10-2001	US 6376476 B1	23-04-2002
			US 6022887 A	08-02-2000
			US 2004106675 A1	03-06-2004
			AU 3100601 A	31-07-2001
			CA 2397659 A1	26-07-2001
			EP 1253922 A2	06-11-2002
			JP 2003527353 T	16-09-2003
			WO 0152829 A2	26-07-2001
			WO 0174180 A1	11-10-2001
			US 6410521 B1	25-06-2002
			US 6080779 A	27-06-2000
			AU 729793 B2	08-02-2001
			AU 5798198 A	03-07-1998
			CA 2274789 A1	18-06-1998
			EP 0944312 A1	29-09-1999
			JP 2001506635 T	22-05-2001
			WO 9825460 A1	18-06-1998
WO 2004024165	A	25-03-2004	AU 2003270154 A1	30-04-2004
			CA 2497182 A1	25-03-2004
			WO 2004024165 A1	25-03-2004
			EP 1539186 A1	15-06-2005